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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,030	11/17/2003	Alain Friboulet	16773-002001 / B4852AF-AD	5572

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EXAMINER	
HARLE, JENNIFER I	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/716,030	FRIBOULET ET AL.	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6 and 22-27* is/are pending in the application.

4a) Of the above claim(s) *6,23,24,26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,22 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

JIH

DETAILED ACTION

Claims 1-23 were pending. Claims 2-4 and 7-21 were canceled and claims 24-27 were added by Applicants' Amendment, filed November 17, 2003. Claims 1, 5-6, 22-27 are pending.

Election/Restrictions

1. Applicant's election without traverse of Group II in the reply filed on December 10, 2004 is acknowledged. However, the Applicant's election of Group I in the reply filed on September 10, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been that election would also have been treated as being without traverse (MPEP § 818.03(a)). Applicants' mere submission that there has been no showing of burden of search, without any specifics is insufficient, given the examiner's statements on the divergent searches required in literature, patent, internet, structure and/or sequence searches of multiple databases with multiple synonyms and key word searches and the plethora of compounds involved.

2. Applicants' request rejoinder of the pharmaceutical compounds claims 22 and 23 stating that they read on the elected compound. However, this is incorrect. The compound selected was not an election of species but the selection of a specific composition containing the elected components, to which the elected invention will be examined on the merits as drawn to. See pg. 9 of the Election/Restriction Requirement. This Election/Restriction Requirement specifically states that "[t]this requirement is not to be taken as an election of species, but rather as a selection of a single invention, since each compound is assumed to be a patentably distinct invention, in absence of evidence to the contrary." Id. at pg. 9. Applicants' elected without traverse and did not provide a specific "further molecule" that modifies or stimulates the

biological activity of a compound comprising LNNRA or diminishes any secondary effects of said compound. Therefore, the examiner will rejoin only claim 22. Moreover, Claim 23 is not drawn to the specific invention as set forth on page 9 of the Election/Restriction requirement.

3. Claims 6, 23-24, and 26-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 10, 2005.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, no that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas,

> etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention.*

In the instant case, the claims are drawn to a compound with the functional features that it modulates (either up-regulates or down-regulates) the activity of a catalytic antibody, the compound has a specific affinity for a catalytic site of the antibody, is non immunogenic and is a ligand that binds to a receptor.

(1) Level of skill and knowledge in the art:

The level of skill and knowledge in the art is that of a PhD scientist and as stated in Applicants' specification there has been work utilizing haptens that can induce the in vivo production of catalytic antibodies, immunization strategies, the site-directed modification of antibodies or screening methods and selection, which are applicable on a case by case basis. Specification pg. 4.

(2) Partial structure:

The claims contain no partial structure. The compound is only described by what it modulates, i.e. the catalytic antibody. The catalytic antibody can be any catalytic antibody and no structure or description of how to find which specific catalytic antibody. The compound is also described by the specific affinity it has for a catalytic site of the antibody but if the antibody itself is unknown then there is no way to know which site on the antibody will be known. It is non immunogenic but that does not significantly limit the structure, as any pharmaceutical could potentially meet that definition. It is a ligand that binds to a receptor. Neither the binding motif nor the receptor is identified. Applicants' do provide some description of a ligand, which is a fragment of TNS-alpha falling within the definition of the compounds of the invention and **capable** of binding to cell receptor p55 and p75, particularly three specific peptide cores that are derived from TNF-alpha that they state are non immunogenic and have a specific affinity for the

catalytic site of a catalytic antibody which contain the following amino acid sequences: LNRRA, IASVY or LFA. See Specification pg. 9. The examiner again notes that the catalytic antibody is not identified nor is the catalytic site of the catalytic antibody identified. Applicants' merely identify a large screening process with large throughput but never identify any compounds. Specification, pp. 12-15. Again there would have to be screening for the ligand/receptor relationship. Thus, there is no relationship shown or demonstrated between the structure – none given and the functions.

(3)/(4)/(5) Physical and/or chemical properties/ Functional characteristics/Method of Making:

The physical/chemical properties and/or functional characteristics are all that describe the compound, for the generic claims. As set forth above, the only structure is set forth when Applicants' do provide some description of a ligand, which is a fragment of TNS-alpha falling within the definition of the compounds of the invention and **capable** of binding to cell receptor p55 and p75, particularly three specific peptide cores that are derived from TNF-alpha that they state are non immunogenic and have a specific affinity for the catalytic site of a catalytic antibody which contain the following amino acid sequences: LNRRA, IASVY or LFA. See Specification pg. 9. However, for the most part, The compound is only described by what it modulates, i.e. the catalytic antibody. The catalytic antibody can be any catalytic antibody and no structure or description of how to find which specific catalytic antibody. The compound is also described by the specific affinity it has for a catalytic site of the antibody but if the antibody itself is unknown then there is no way to know which site on the antibody will be known. It is non immunogenic but that does not significantly limit the structure, as any pharmaceutical could potentially meet that definition. It is a ligand that binds to a receptor. Neither the binding motif

nor the receptor is identified. The examiner again notes that the catalytic antibody is not identified nor is the catalytic site of the catalytic antibody identified. Applicants' merely identify a large screening process with large throughput but never identify any compounds. Specification, pp. 12-15. Again there would have to be screening for the ligand/receptor relationship. Thus, there is no relationship shown or demonstrated between the structure – none given and the functions. The examples set forth are replete with prophetic possibilities, i.e. Example 1 "milk **may have** a catalyic protein kinase, DNase or Rnase type activities ... the production of a catalytic antibody directed against the eptitopes of the Herpes simplex type 1 virus **could be stimulated** by cutaneous application of non immunogenic peptides ... a similar approach **can be applied to stimulate** the production of catalytic antibodies hydrolyzing HSV2 peptides; Example 2 – "non immunogenic peptides having a specific affinity with a catalytic antibody capably of hydrolyzing TNF-alpha were selected from peptides containing the sequences LNRRA (29-33), IASVY (83-87) and (LFA (143-145). Repeated injections of these peptide to a patient suffering from rheumatoid arthritis **should stimulate** *in vivo* the production catalytic antibodies hydrolyzing TNF-alpha in sequences recognizing cell receptors ..."; Example 3 – is directed to immunogenic peptides not non immunogenic peptides; Example 4 – "the lethality linked of repeated injection of penicillin **should be reduced** by stimulating the production of anti-idiotypic antibodies with a beta-lactamse activity by administering non immunogenic peptides ...; Example 5 – "Administering a non immunogenic molecule derived from the allergen to a subject sensitive to an allergen **should modify** the immunological response..."; A Non immunogenic peptides for preventing or diminishing allergies to anti-infectious medication. – 'It is known that allergenicity is primarily carried by the beta-lactame

cycle. By being cleaved during metabolism, the beta-lactame cycle produces the penicilloyl hapten **which is capable of inducing** the production of IgE. **It would thus be possible**, using orally injected non immunogenic peptides that inhibit beta lactamse to induce the production of non IgE antibodies **capable of hyrdrolyzing** antibiotics with a beta-lactame ring, thus preventing the production of IgE antibodies. (Note there are no specific examples of peptides, catalytic antibodies, catalytic sites, etc. and that it is all couched in probabilities and possibilities); B. Non immunogenic peptides stimulating the production of catalytic antibodies hydrolyzing serotonin to prevent or diminish food allergies. Discusses food allergies and that "Serotonin (5-hydroxytryptamine), for example, is derived from tryptophan and degraded into 5-hydroxyindole acetate. **It would thus be possible** to select non immunogenic peptides derived form serotonin and having a specific activity for a catalytic antibody hydrolyzing serotonin. Oral injection of such peptides stimulating the production of catalytic antibody degrading excess serotonin **should reduce** allergic phenomena linked to food." (Note there are no specific examples of peptides, catalytic antibodies, catalytic sites, etc. and that it is all couched in probabilities and possibilities); Example C is set forth with the same lack of specific examples and is couched in the same probablilities and possibilities. Applicants' have not provided one written example that meets the limitations of their claims, they have only provided non immunogenic peptides that are ligands. They have never shown in any particular examples that their ligands modulate catalytic antibodies, let alone at a specific site or that they have even screened to find that this is so or would work in their environment.

As previously set forth there is no relationship between the structure (a compound) and the function(s) modulates a catalytic antibody (can be any catalytic antibody), has a specific

affinity for a catalyic site of the antibody (any site on the antibody), is non immunogenic (no linked to the other functions), and is a ligand that binds to a receptor (not linked to the other functions and can be any receptor/no specificity required).

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, 22, and 25 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Miller, et al. (WO 96/34887).

The claims are drawn to a compound that modulates the activity of a catalytic antibody, wherein said compound has a specific affinity for a catalytic site of said antibody, is non immunogenic, and is a ligand that binds to a receptor, which can be a pharmaceutical composition, and specifically a peptide derived from TNF-alpha comprising LNRRA.

The cited reference teaches a composition (including in pill/tablet form) derived from TNF-alpha, which is the active region 29-34, LNRRAN, which is known to be critical in binding to the p75 receptor only, i.e. a ligand which is derived from TNF-alpha and is non immunogenic, as is its complement, also derived from TNF-alpha, which can be administered in anti-cancer

therapy without the systemic toxicity dependent on p75 activation, therein which appears to be identical to (and thus anticipate) the presently claimed compound derived from TNF-alpha, comprising LNNRA pharmaceutical (including inherently comprising the instantly claimed modulation of the catalytic antibody with a specific affinity for a catalytic site of said antibody) since both are similar peptides (including the same core sequence LNRRA with only one additional amino acid) and are derived from the same source materials – TNF-alphas, and both demonstrate the same/similar activity with respect to binding the same receptor p75 (see pg 23). Consequently, the instantly claimed compound appears to be anticipated by the cited reference. See specifically pp. 23-24 and claims and 1-24.

In the alternative, even if the claimed compound, particularly the compound derived from TNF-alpha, more particularly comprising LNRRA, is not identical to the referenced compound with regard to some unidentified characteristics, the differences between that which is disclosed and that which is claimed are considered to be so slight that the referenced compound is likely to inherently possess the same characteristics of the claimed compound particularly in view of the similar characteristics which they have been shown to share. Thus, the claimed compound would have been obvious to those of ordinary skill in the art within the meaning of USC 103.

Accordingly, the claimed invention as a whole was at least prima facie obvious, if not anticipated by the reference, especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Please note that the Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether the compound modulates catalytic antibodies/has a specific affinity for a catalytic site of the antibody disclosed by the cited reference. Therefore,

with the showing of the reference, the burden of establishing non-obviousness by objective evidence is shifted to the Applicants.

Please also note that "the patentability of a product does not depend upon its method of production. Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 218 USPQ 289, 292 (Fed. Cir. 1983).

Conclusion

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Hans-Joachim Bohm, et al. (DE 3841767 A1) – New TNF –Peptide – discloses Sequences comprising LNRRA for example No. 39 on pg. 1; Analog Example 55 on Pg. 13, line 61 on pg. 13, etc.;

Hans-Joachim Boehm (WO 90/06939) – New TNF Peptides – discloses Sequences comprising LNNRA, Pp. 1, 3, 19, 21, 24.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer I. Harle
Examiner
Art Unit 1654

April 4, 2005